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在线全文

# 骨-血管轴共病动物模型研究进展*

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【摘要】 骨质疏松与心血管钙化是当今中国社会常见的两个重大老年性慢病，严重危害公共健康。现有研究表明，这两种疾病在病理进程和分子机制上存在交叉联系，尤其在炎症、氧化应激以及矿物质代谢失调等方面，往往有共同的致病因素。然而现有研究对两种疾病的共病机制探索不够深入和广泛，限制其深入研究的因素可能是缺乏被广泛认可的共病动物模型。本文分析了血管钙化和骨质疏松共病机制的最新研究进展，并侧重总结当前广泛应用的动物疾病模型和相关评价标准，为共病研究模型提供新的参考，同时为未来的病理机制研究和新的治疗策略开发提供科学依据。

【关键词】 血管钙化 骨质疏松 动物模型 综述

# Advances in Animal Modeling in the Study of Bone-Vascular Axis Comorbidities

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[**Abstract**] Osteoporosis and cardiovascular calcification, two major age-related chronic diseases that China is confronting today, pose serious threats to public health. Previous studies have reported overlapping connections in the pathological processes and molecular mechanisms of these two diseases, particularly concerning inflammation, oxidative stress, and dysregulation of mineral metabolism, and that these two diseases tend to share common pathogenic factors. However, research exploring the comorbidity mechanisms of the two diseases remains limited in both depth and scope, largely due to the lack of widely accepted comorbidity animal models. Herein, we analyzed the latest research findings on the comorbidity mechanisms of vascular calcification and osteoporosis, focusing on summarizing the animal disease models currently in extensive use and the relevant evaluation criteria. We aim to provide new references for comorbidity research models and offer scientific evidence for future studies on pathological mechanisms and the development of new therapeutic strategies.

[**Key words**] Vascular calcification Osteoporosis Animal models Review

骨质疏松是死亡率增加的重要公共卫生问题。有研究表明，低骨量的心血管疾病患者死亡率高于正常骨量的患者[1]。骨质疏松症的特点是骨稳态的变化导致骨量减少、骨质量受损和骨折风险增加[2]。骨质疏松症患者同时患心血管钙化的风险增高，某项研究中对骨质流失和血管钙化进行了30年的纵向分析，结果显示在掌骨处测量的皮质骨流失与女性主动脉粥样硬化钙化的进展相关[3]。某些骨转换异常会影响血管健康，最近的研究表明，钙化血管释放的因子也会导致慢性肾病（chronic kidney disease, CKD）的骨骼恶化[4]。低骨密度与心血管疾病发病率和死亡率增加有关[5-6]。衰老、雌激素缺乏、维生素D和维生素K异常、微量元素缺少、慢性炎症和氧化应激都可能会导致骨质流失和血管钙化[7-12]。一般认为炎症、氧化应激和一些促钙化因子（如磷酸盐、钙）是关键诱导因素[8]。血管钙化是钙和磷酸盐在心血管异位沉淀的过程，往往涉及血管平滑肌细胞（vascular endothelial smooth muscle cells, VSMCs）向成骨细胞样细胞的转变[13]。其源于遗传风险、环境因素和与衰老相关的生物学变化的综合作用[14]。CKD患者骨骼去矿化和血管钙化常常是相辅相成的，这与普通人群中的情况类似。这种矛盾的关联与年龄无关，通常被称为“钙化悖论”[15]。骨质疏松和血管钙化之间关系复杂，需使用各种研究工具使临床医生和科学家能够更仔细地研究这两种疾病背后的分子和细胞机制[16]。很多机制仍无法通过人体研究直接解析，所以，动物模型是研究这两种疾病的首选工具。在探讨血管钙化与骨质疏松的共病关系时，研究者通常需要结合两种疾病的动物模型，设计一个可以同时呈现血管钙化和骨质疏松特征的共病模型。通过这

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种模型，研究者可以在单一实验中同时观察这两种疾病的相互影响。传统的生物标志物存在低特异性、低敏感性和研究结果相互矛盾等局限性[17]。因此缺乏适合的动物模型能够同时反映两种疾病的变化过程。本文通过系统性梳理血管钙化与骨质疏松的动物模型，为后续研究提供参考。

## 1 骨质疏松和血管钙化的病理机制

### 1.1 骨质疏松症的发病机制

骨质疏松症(osteoporosis, OP)是一种系统性骨骼疾病，特征是骨矿物质流失和骨小梁与皮质骨微结构的改变，导致骨骼强度下降，易发生骨折[4]。OP一型主要发生在绝经后妇女中，通常由于雌激素缺乏引起；二型则多见于老年人群，可能与年龄相关的骨代谢紊乱和维生素D缺乏等因素有关。OP的发生与破骨细胞的活跃增高密切相关，常通过RANK/RANKL/OPG信号通路进行调控[4]。

### 1.2 血管钙化的发病机制

血管钙化(vascular calcification, VC)是指钙盐在血管壁内的异常沉积，主要与动脉硬化、炎症和脂质沉积和钙磷代谢紊乱以及VSMCs向成骨样表型转化相关[2]。VSMCs的转化是血管钙化的关键过程，VSMCs由收缩型表型转变为成骨型表型，导致钙磷盐在血管壁内沉积，从而引发血管僵硬和弹性丧失，影响血液流动和血管功能[13]。

### 1.3 血管钙化与骨质疏松症的共病机制

近年来有研究发现，老年人群常同时患有血管钙化与骨质疏松症，并且这两种疾病有部分相似的病理机制。甲状旁腺激素(parathyroid hormone, PTH)、RANK/RANKL/OPG通路、Wnt/β-catenin信号通路在这两种疾病的共病调节中起关键作用。

#### 1.3.1 钙磷调节激素的共调节作用

PTH双向调控：PTH通过调节骨吸收与肾小管的钙重吸收以维持血钙平衡。在骨质疏松症中，PTH持续升高会激活破骨细胞，加剧骨丢失；在血管钙化中，PTH通过激活VSMCs中的环磷酸腺苷(cAMP)信号，促进碱性磷酸酶(ALP)表达和钙盐沉积。PTH受体(PTH1R)在VSMCs中的异常表达可加速血管钙化，形成“高PTH-骨丢失-血管钙化”恶性循环[4, 8]。

FGF23/Klotho轴：骨细胞分泌的FGF23，通过Klotho受体抑制肾小管对磷的重吸收，降低血磷水平。Klotho蛋白减少氧化应激并增强细胞的抗衰老能力，在CKD中，Klotho表达下调导致FGF23抵抗，引发高磷血症，促进血管钙化；FGF23通过抑制1,25-二羟维生素$D_3$合成，减少肠道钙吸收，促进骨矿化。FGF23/Klotho轴通过调节Wnt/β-catenin和NF-κB信号通路，抑制血管平滑肌细胞向成骨细胞的转化，从而抑制血管钙化，同时该轴也通过调节维生素D和磷的代谢，促进骨矿化和骨重塑，有效预防骨质疏松[7]。

维生素D与维生素K的协同效应：维生素D以活性形式1,25-二羟维生素$D_3$促进肠道钙吸收和肾小管钙重吸收维持血钙水平，但过量会刺激VSMCs向成骨样细胞转化，诱导血管钙化。维生素K的羧化作用可激活蛋白〔如基质Gla蛋白(MGP)和骨钙素(OCN)〕，不仅抑制血管壁中的钙沉积，还促进钙的从血液向骨组织的转运，从而增强骨矿化和骨强度[9]。维生素K缺乏时，非羧化MGP(ucMGP)蓄积于血管壁，失去抑制钙沉积的能力，同时非羧化OCN(ucOCN)会降低骨矿化效率。

#### 1.3.2 骨髓脂肪化与血管钙化的相互作用

骨髓脂肪化的病理影响：骨髓间充质干细胞(BMSCs)在衰老或雌激素缺乏状态下倾向于分化为脂肪细胞而非成骨细胞，会导致骨髓脂肪组织积累。这种脂肪化微环境释放游离脂肪酸(FFAs)和炎症因子(如IL-6、TNF-α)，抑制成骨细胞活性并激活破骨细胞，加剧骨质疏松[18]。

脂肪因子介导血管钙化：骨髓脂肪细胞分泌脂联素和瘦素等脂肪因子。脂联素可通过AMPK通路抑制VSMCs钙化，但其在骨髓脂肪化中表达降低，会丧失保护作用。瘦素可激活RANKL/OPG通路，促进破骨细胞生成，同时通过JAK2/STAT3信号诱导VSMCs成骨样转化[19]。

过氧化物酶增殖物激活的受体γ(PPARγ)信号：PPARγ是脂肪分化的关键转录因子。PPARγ激动剂(如噻唑烷二酮类药物)可改善胰岛素抵抗，但会加剧骨髓脂肪化和骨丢失，并增强BMP2表达促进血管钙化[18]。

#### 1.3.3 骨代谢相关分子对血管钙化的调控

骨形态发生蛋白(BMPs)的双重作用：BMP2在骨形成中促进成骨分化，但在血管中通过Smad1/5/8通路诱导VSMCs成骨样转化，导致钙沉积。BMP2抑制剂可减轻血管钙化。BMP7可拮抗BMP2作用，维持血管稳态，但其表达在CKD中显著降低，加剧钙化[13]。

OCN的调控：羧化OCN(cOCN)是骨矿化的标志物，而ucOCN作为激素分子进入循环，通过GPRC6A受体激活胰岛β细胞和睾丸间质细胞功能。在血管中，ucOCN通过抑制NF-κB通路减少炎症因子释放，间接抑制钙化；但其在骨质疏松患者中水平降低，导致血管保护作用减弱[9]。

细胞外囊泡(EVs)的介导作用：老化骨基质衍生的细胞外囊泡可能通过释放特定的miRNA或蛋白质影响钙化相关基因的表达，这种机制表明血管和骨骼的微环境交互有着重要作用[18, 20]。

此外, Nrf-2、AMPK、SIRT1蛋白通过调控氧化应激、炎症及细胞自噬等生物过程, 在防止慢性肾病相关的血管钙化过程中发挥关键作用。Nrf-2抑制氧化应激和钙化基因; AMPK通过提升能量代谢激发SIRT1的活性, 而SIRT1则通过改善内皮功能和抑制钙化来维护血管健康[11, 21]。镁元素通过抑制Wnt/β-catenin和TGF-β通路来减少血管钙化, 同时激活Wnt/β-catenin和mTOR通路促进骨生成和矿化[12]。

这些相互作用的深入研究不仅增强了对这两种疾病共病机制的认识, 也为开发新的、针对血管钙化和骨质疏松的共病动物模型提供参考。

## 2　动物研究模型

### 2.1　骨质疏松的动物模型

近5年来常见的骨质疏松动物模型包括卵巢切除(ovariectomized, OVX)模型、低钙饮食模型以及转基因模型(如*Col1a1*突变小鼠)等, 详见表1。

骨质疏松动物模型的构建方式多样, 其中最常用的为卵巢切除术(图1)、糖皮质激素刺激和悬尾模型。相比传统的动物模型, 基因改造小鼠模型提供了深入研究分子机制的可能。

### 2.2　血管钙化的动物模型

常见的血管钙化的动物模型包括高钙饮食、慢性肾病小鼠模型、糖尿病模型和基因敲除模型(如*MGP*缺失小鼠)。本文总结了近5年内广泛报道的动物模型, 归类如表2。

血管钙化动物模型(图2)主要通过高磷饮食、部分肾脏切除和基因编辑技术构建。基因敲除小鼠模型, 如*Apoe* KO和*Ldlr* KO, 广泛用于研究脂质代谢和钙化机制。近年来, 发现了多种与血管钙化相关的关键基因, 包括

**表 1　骨质疏松的动物研究模型**

**Table 1　Animal research models of osteoporosis**

| Model | Method | Pathogenic mechanism | Disease | Modeling period | Reference |
|---|---|---|---|---|---|
| Classical model (rat/mouse) | Ovariectomy | Ovariectomy is performed to mimic postmenopausal estrogen deficiency-induced bone loss. | Osteoporosis | 4-12 weeks | [22-24] |
| | Glucocorticoids | Glucocorticoids inhibit osteoblast proliferation and function, reducing bone matrix synthesis. | Osteoporosis | 8 weeks | [25] |
| | Tail suspension | The tail is suspended to mimic reduced mechanical loading and gravity effects in aging, leading to bone loss. | Bone metabolism | 4-12 weeks | [26] |
| Classical model (sheep) | Ovariectomy | Ovariectomy is performed to mimic postmenopausal estrogen deficiency-induced bone loss. | Osteoporosis | 12/24 months | [27] |
| Mechanical induction (rat/mouse) | Resistance exercise | Resistance exercise alleviates osteoporosis symptoms in ovariectomized rats. | Osteoporosis | 4-12 weeks | [28] |
| | Special environment (cadmium exposure) | Cadmium exposure induces bone defects. | Bone defects | 3/4 months | [29] |
| Mechanical induction (dog) | Neurectomy | Sciatic neurectomy disrupts both sensory and motor branches, thereby inducing disuse by a complete faccid paralysis. | Bone defects | 14-36 d | [30] |
| Drug induction (rat/mouse) | Teriparatide | Bisphosphonates and teriparatide alter miRNA levels in bone and blood during treatment. | Osteoporosis | 12-20 weeks | [31] |
| | Puerarin | Puerarin inhibits RANKL-induced osteoclast differentiation in bone marrow macrophages and RAW264.7 cells. | Osteoporosis | 12-20 weeks | [32] |
| | Tobacco toxin | Tobacco toxin induces bone marrow mesenchymal stem cell aging by inhibiting mitophagy. | Bone aging | 12-20 weeks | [33] |
| | Quercetin | Quercetin alleviates osteoblast apoptosis by activating the PI3K-AKT signaling pathway. | Osteoporosis | 12-20 weeks | [34] |
| Drug induction (zebrafish) | Alloxan | Alloxan causes the apoptosis of pancreatic islet β cells in zebrafish, which leads to osteoporosis. | Osteoporosis | 4 months | [35] |
| Genetic engineering (mouse) | Gene knockout (*Foxf1* KO) | Foxf1 activates Wnt/β-catenin signaling in bone marrow mesenchymal stem cells to reduce bone loss. | Bone loss | 6 weeks | [36] |
| | Gene knockout (*SIRT2* KO) | SIRT2 regulates liver-bone communication via extracellular vesicles. | Osteoporosis | 6 weeks | [37] |
| | Gene knockout (*ENPP1* KO) | ENPP1 deficiency affects bone mass and mineralization. | Bone metabolism | 70/161 d | [38] |
| | Gene knockout (*VDR* KO) | Vitamin D receptor activation alleviates ferroptosis and senescence in osteoblasts. | Osteoporosis | 3 months | [39] |
| | Transgenic (*RANKL* overexpression) | Bone marrow adipose tissue-derived RANKL mediates bone resorption. | Osteolysis | 4 weeks-8 months | [18] |
| Genetic engineering (zebrafish) | Gene knockout (*GGPS1* KO) | GGPS1 and ATRAID promote the function of osteoclasts. | Osteoporosis | 28 months | [40] |

KO: knock out; VDR: vitamin D receptor.

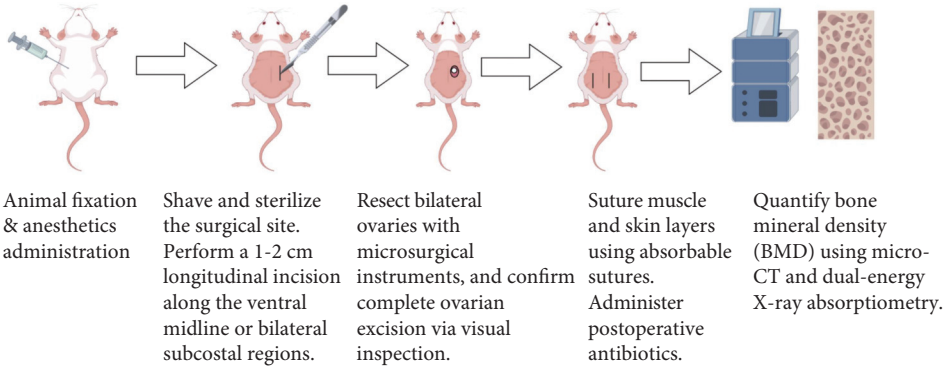


**图 1 骨质疏松经典动物模型构建流程图**

**Fig 1 Flow chart of the construction of the classic animal model of osteoporosis**

**表 2 血管钙化的动物研究模型**

**Table 2 Animal models of vascular calcification**

| Model | Method | Pathogenic mechanism | Disease | Modeling period | Reference |
|---|---|---|---|---|---|
| Classical model (Fig.2) | High-fat diet and partial nephrectomy | Partial nephrectomy is performed to mimic renal dysfunction-induced calcium-phosphate imbalance. | CKD, uremia, and chronic renal failure | 8-12 weeks | [18, 41-42] |
| | High-fat diet and *APOE* KO | *APOE* KO mice develop lipid metabolism disorders and vascular calcification. | Vascular calcification | 4-20 weeks | [43] |
| | High-phosphate/sugar/fat diet | High-phosphate/sugar/fat diets promote vascular calcification. | CKD, diabetes, and hyperlipidemia | N | [43-46] |
| Dietary induction | Magnesium-supplemented diet | Magnesium improves mitochondrial function and antioxidant capacity to reduce vascular calcification. | Vascular calcification and progeria | 8 weeks | [47-48] |
| | Special diet: Iron-dextran injection | Iron overload induces calcium deposition. | Renal failure and vascular calcification | 4 weeks | [49-50] |
| Dietary induction (monkey) | Alloxan injection | Injection of alloxan can destroy the insulin-producing β-cells of the pancreas. | Vascular calcification | 5-6 yesrs | [50] |
| Dietary induction (rabbit) | Iron injection | Iron overload induces calcium deposition. | Vascular calcification | N | [51] |
| Mechanical induction | Surgical intervention (Hydrogel composite implant | Hydrogel-tissue composites reduce calcification in cardiovascular implants. | Anti-calcification therapy | 45 d | [52] |
| Genetic engineering | Gene knockout (*Klotho* KO) | *Klotho* deficiency disrupts FGF23 signaling and calcium-phosphate metabolism. | Vascular calcification | 8 weeks | [48] |
| | Gene knockout (*Abcc6* KO) | Vitamin D and calcium supplements accelerate calcification in *Abcc6* KO mice (pseudoxanthoma elasticum). | Pseudoxanthoma elasticum | 6 months | [53] |
| | Gene knockout (*AIF-1* KO) | Aldosterone-induced vascular calcification via *AIF-1* signaling in CKD. | CKD | 16-18 weeks | [54] |
| | Gene knockout (*STIM1* KO) | Smooth muscle cell-specific *STIM1* deletion disrupts calcium homeostasis and endoplasmic reticulum stress in diabetes. | Diabetes | 14 weeks | [55] |
| | Gene mutation (*Lmna*) | *Lmna* mutation impairs redox balance and mitochondrial function in progeria. | Progeria syndrome | N | [47] |
| | Gene mutation (*ENPP1*) | *ENPP1* mutation causes systemic arterial calcification. | Systemic arterial calcification | N | [56] |
| | Transgenic (*MSX1* and *MSX2*) | *MSX1/2* promotes vascular calcification by activating MDM2. | Vascular calcification | 8-N | [57] |
| | Transgenic (*Tyk2*) | *Tyk2* deficiency inhibits calcification-related gene expression and signaling pathways. | CKD | 8-N | [58] |
| Genetic engineering (rabbit) | Gene knockout (*APOE* KO) | *APOE* KO rabbit develops lipid metabolism disorders and vascular calcification. | Vascular calcification | N | [59] |
| *Ex vivo* model | *Ex vivo* model (Porcine heart) | Simulation of human vascular calcification *in vitro*. | Vascular calcification | N | [60] |

KO: knock out; CKD: chronic kidney disease.

*TDAG51*、*GSK343*、*NR4A3*、*K176*、*BRCC36*和*GDF10*等[61-66]。这些基因通过多种机制调控血管钙化过程。例如，*TDAG51*在细胞凋亡中发挥重要作用，其表达上调被认为是诱导钙化的关键环节[61]；*GSK343*通过调控组蛋白甲基化影响

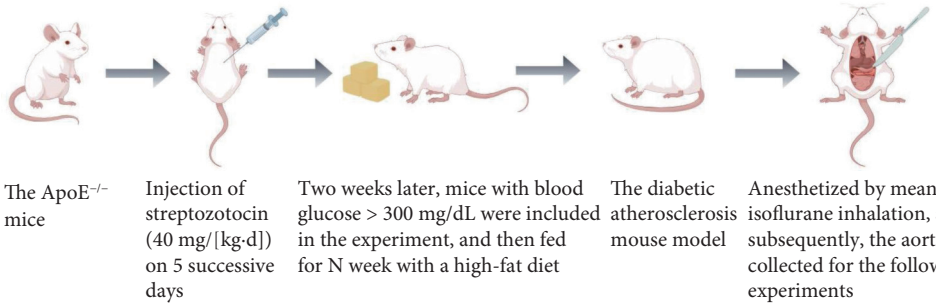


**图 2　血管钙化经典动物模型构建流程图**

**Fig 2　Flow chart of constructing the classical animal model of vascular calcification**

平滑肌细胞的表型转换, 从而促进钙化[62]; *NR4A3*则通过调节炎症信号通路, 改变钙化微环境[63]; *K176*和*BRCC36*的功能失调被发现显著干扰细胞自噬和钙离子代谢的平衡[64-65]; 而*GDF10*则通过影响成骨相关信号通路直接参与钙沉积的形成[66]。这些基因的作用机制各异, 但都和血管钙化密切相关, 有望作为新的动物模型构建的基因敲除靶点。

## 3　骨质疏松与血管钙化的共病模型

目前被广泛认可的骨质疏松和血管钙化的共病动物模型较少, 这些研究中所使用的共病动物模型包括但不限于通过激素水平的改变、基因表达的调控和药理学干预来构建模型以模拟人类疾病的进程。在针对血管钙化与骨质疏松之间的关联性研究中显示细胞因子如骨保护蛋白(osteoprotegerin, OPG)和受体活化核因子κB配体(receptor activator of nuclear factor κB ligand, RANKL)在调节这两种病理过程中的重要作用。一项研究中使用*OPG*基因敲除小鼠(*OPG* KO)模型, 这些小鼠会出现明显的动脉钙化和严重的高周转骨质丢失。这项研究中发现omentin-1通过抑制RANKL的表达而在*OPG*缺失的小鼠模型中减轻动脉钙化和骨质流失, 揭示了该蛋白在血管生物学中的潜在保护作用[67]。

同时, 有研究通过对*ENPP1*基因功能研究的进一步深入, 了解到该基因在调节骨骼健康和动脉钙化中的关键作用。进而构建出*ENPP1* KO的小鼠模型, 以研究其在血管钙化和骨质疏松中参与调节的通路[38]。在另一项类似的研究中研究人员利用Enpp1$^{asj/asj}$小鼠模型, 来研究人类早发性骨质疏松症的特征。这种模型中, 小鼠的*Enpp1*基因发生突变, 导致无法有效地产生足够的焦磷酸盐, 从而抑制体内矿物质沉积。这种基因的突变和功能缺失与人类的一些遗传性疾病相对应, 如一般性动脉钙化病和常染色体隐性低磷血症性佝偻病2型[68]。

有关内分泌调节血管钙化和骨质疏松的研究中对小鼠模型进行了OVX, 以模拟绝经后妇女的雌激素缺乏状态, 然后给予高脂饮食持续3个月, 用以诱发动脉粥样硬化和钙化。该研究揭示了雌激素通过调节血管中的RANKL信号系统来抑制血管钙化的机制。表明雌激素可以抑制RANKL引起的主动脉内皮细胞中BMP-2的表达, 进而减少钙沉积的形成[69]。另一项类似的研究中使用维生素$D_3$和尼古丁处理的OVX大鼠模型。研究发现OVX加VDN〔vitamin D(3) plus nicotine〕处理的大鼠在治疗后8周显示出动脉钙化和骨质流失的特征, 而单独OVX的对照组则只表现出骨质流失。该研究有效地揭示了绝经后妇女可能经历的动脉硬化与骨质疏松之间的流行病学联系[70]。

这些动物模型和技术为开发针对血管钙化和骨质疏松共病的治疗策略提供了基础, 有望推动这一领域的研究进展, 为未来的治疗提供新的方向。

## 4　骨-血管轴共病动物模型的标准化评价标准

由于目前的骨-血管轴共病动物模型较少, 还没有准确的标准化评价标准, 因此笔者参考了近5年研究及行业指南以及其他相关实验文献, 总结出了有关骨质疏松(表3)和血管钙化(表4)的动物模型评价标准, 以作为后续骨-血管轴共病动物模型标准的参考。在实际运用时, 骨质疏松动物模型中部分阈值(如骨密度下降水平, 血清钙磷水平)可能因动物品系、建模方法差异需调整, 实验结果需结合骨密度测定(DEXA/pQCT)、生物化学指标〔骨碱性磷酸酶(BAP)、抗酒石酸酸性磷酸酶(TRAP)〕、骨形态学分析及生物力学测试(三点弯曲试验)等综合评估, 建议使用至少两种模型和不同种属动物进行验证, 以提高结果的可靠性[71]。血管钙化动物模型的关键验证标准为: ①病理学: 钙化面积≥10%(Von Kossa染色), 弹性纤维评分≥2级; ②影像学: Agatston评分≥11(中度), Kauppila评分≥4; ③生化指标: 血清钙/磷显著升高($P$< 0.05), ALP活性升高≥30%; ④功能评估: 脉搏波速度

表 3 骨质疏松动物模型评价标准

Table 3 Standardized evaluation criteria for osteoporotic animal models

| Category | Animal model type | Osteoporosis criteria |
|---|---|---|
| Hormone intervention | Ovariectomy model | BMD reduction (20%-30% in femur/spine), decreased trabecular volume, and significant drop in serum estradiol/testosterone. |
| | Glucocorticoid-induced model | BMD reduction (15%-25%), trabecular thinning, and reduced biomechanical strength (30%-40% drop in 3-point bending load). |
| Disuse induced | Suspension model | Hindlimb BMD reduction (10%-15%), calcium-phosphorus imbalance, and reduced trabecular connectivity. |
| Nutritional deficiency | Low-calcium diet model | Tibial/vertebral BMD reduction (15%-25%) and elevated serum BAP and TRAP (30%-50%). |
| Other types | Streptozotocin-induced model | Reduced bone alkaline phosphatase activity (—30%) and trabecular structural damage (20%-25% volume loss). |
| | Genetic engineering model | The deletion of target gene expression was verified by qPCR or Western blot. |
| | Combined modeling approach | BMD reduction (20%-30%), trabecular volume loss (30%-40%), and elevated bone resorption markers (CTX-Ⅰ: 50%-100% increase). |

表 4 血管钙化动物模型评价标准

Table 4 Standardized evaluation criteria for vascular calcification animal models

| Category | Animal model type | Calcification criteria |
|---|---|---|
| Imaging evaluation | CT scan (Agatston score) | 0: No calcification<br>1-10: Minimal (early stage)<br>11-100: Mild<br>101-400: Moderate<br>> 400: Severe |
| | X-ray (Kauppila score) | 0-3: Mild<br>4-6: Moderate<br>⩾ 7: Severe |
| Histopathological analysis | Von Kossa staining | Mild: < 10% calcified area<br>Moderate: 10%-30%<br>Severe: > 30% |
| | Elastic fiber staining | 0: None<br>1: Focal points<br>2: Localized<br>3: Patchy<br>4: Full-layer calcification |
| Biochemical markers | Serum calcium/Phosphorus | Ca > 2.5 mmol/L, $PO_4$ > 3.0 mmol/L (significant increase, $P < 0.05$) |
| | Alkaline phosphatase (ALP) | ⩾ 30% increase |
| | Tartrate-resistant acid phosphatase (TRAP) | ⩾ 20% increase |
| Functional assessment | Pulse wave velocity (PWV) | PWV > 5 m/s |
| | Biomechanical testing | ⩾ 30% reduction in load-bearing capacity |
| Others | Genetic engineering model | The deletion of target gene expression was verified by qPCR or Western blot. |

(PWV)> 5 m/s或生物力学强度下降⩾30%。实验结果应根据具体的实验需要结合影像学、病理学、生化和功能检测进行综合评价[72]。

## 5 骨-血管轴共病动物模型与人类疾病差异的描述和临床转化前景

### 5.1 动物模型与人类疾病的主要差异

小鼠、大鼠等动物的骨代谢速率明显快于人类(小鼠骨重塑周期约为21 d, 人体为3 ~ 4个月), 导致骨质疏松模型的骨丢失速度远超人体自然病程。小鼠主动脉壁厚度仅为人类的1/10, 缺乏人类动脉粥样硬化斑块中的纤维帽结构, 其血管钙化的病理特征与人类存在明显差异, 如钙化结节分布等。在基因编辑模型中, 如*OPG* KO或*Klotho* KO小鼠模型能模拟特定基因缺陷相关的共病表现, 但人类骨质疏松和血管钙化多为多基因、多环境因素共同作用的结果, 单基因模型难以全面反映临床疾病的复杂性。高磷饮食或过量维生素D诱导的模型可快速诱导血管钙化, 但不能反映CKD中钙磷代谢紊乱与炎症、氧化应激的长期作用。动物模型常通过急性炎症(如LPS注射)模拟慢性炎症, 但人类血管钙化更多与低度慢性炎症(如IL-6、TNF-α持续升高)相关, 二者在细胞因子谱和信号通路上存在显著差异[66]。

### 5.2 临床转化前景

可开发更贴近人类的多因素模型, 如猪或非人灵长类动物等大动物模型, 这些动物的心血管和骨骼系统更接近人类, 更适合模拟老年性共病(如结合高脂饮食+肾切除+衰老诱导)。或者利用患者来源的骨-血管共培养类器官, 动态模拟钙磷代谢交互作用, 减少种属差异影

响。还可结合多组学与人工智能: 通过转录组、蛋白质组和代谢组数据整合, 筛选跨物种保守的病理靶点(如*RUNX2*、*BMP-2*), 使用AI辅助设计个性化治疗方案[42]。

## 6　总结及展望

本文系统性地梳理了近5年的骨质疏松与血管钙化动物模型的建模方法, 归纳出常见的动物模型, 认为基因编辑技术在新型动物模型构建中具有巨大潜力, 同时推测了未来基因改造的潜在动物模型, –为血管钙化和骨质疏松共病动物模型的建立提供参考。

目前共病研究还很缺乏, 有许多未知。未来的研究可以发展更复杂的动物模型, 结合骨质疏松和血管内疾病的症状, 以更加真实地模拟临床中多因素共病的环境。这种多因素共病模型能够揭示不同病理因素在血管钙化和骨质疏松发展中的协同作用, 为复杂病例提供更多治疗策略的参考。

*　　*　　*

**作者贡献声明**　李佳阳负责论文构思、研究方法、初稿写作和审读与编辑写作, 周雨萌负责论文构思、研究方法和审读与编辑写作, 罗钰雯和黄雪琳负责论文构思和审读与编辑写作, 张德茂负责论文构思、数据审编、正式分析、监督指导、初稿写作和审读与编辑写作, 刘肖珩负责论文构思和审读与编辑写作。所有作者已经同意将文章提交给本刊, 且对将要发表的版本进行最终定稿, 并同意对工作的所有方面负责。

**Author Contribution**　LI Jiayang is responsible for conceptualization, methodology, writing--original draft, and writing--review and editing. ZHOU Yumeng is responsible for conceptualization, methodology, and writing-- review and editing. LUO Yuwen and HUANG Xuelin are responsible for conceptualization and writing--review and editing. ZHANG Demao is responsible for conceptualization, data curation, formal analysis, supervision, writing--original draft, and writing--review and editing. LIU Xiaoheng is responsible for conceptualization and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

**利益冲突**　本文作者刘肖珩是本刊编委会编委。该文在编辑评审过程中所有流程严格按照期刊政策进行, 且未经其本人经手处理。除此之外, 所有作者均声明不存在利益冲突。

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